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Down syndrome in Eastern Libya: Cytogenetic subtypes, age at diagnosis, and maternal age in a five-year series

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Abstract: Down syndrome is the most common autosomal aneuploidy, but its cytogenetic subtypes and the age at which it is diagnosed have not been well described for eastern Libya. This study characterized the Down syndrome cases within a five-year cytogenetic registry, with attention to subtype distribution, age at diagnosis, and maternal age. This study analyzed the Down syndrome cases identified among all karyotype referrals to the Genome Laboratory, Benghazi, in 2021-2025, the subset of a 319-record registry whose overall cytogenetic profile is reported separately. Karyotypes were classified per ISCN as free trisomy 21, translocation, or mosaic. Maternal age was compared between Down syndrome and other referred patients using the Mann-Whitney U-test; proportions are given with 95.0% confidence intervals (CIs). 58 patients had Down syndrome (23.1% of 251 karyotyped referrals; 31 male, 27 female). Free trisomy 21 accounted for 54 cases (93.1%; 95.0% CI 83.6-97.3), translocation for three (5.2%), and mosaicism for one (1.7%). Diagnosis was early: The median age at karyotyping was 0.10 years (about five weeks), and 50 of 56 patients with a recorded age (89.3%) were diagnosed before their first birthday. The median maternal age was 37.0 years (interquartile range 31-41), with 58.6% of mothers aged 35 years or older; maternal age was higher than among other referred patients (median 31.0 years; $p = 0.008$). The subtype distribution matched international and earlier Libyan data and differed from a recent Benghazi series that reported markedly higher mosaicism. Thus, in eastern Libya, Down syndrome is predominantly free trisomy 21, is strongly associated with advanced maternal age, and, unlike the sex-chromosome aneuploidies, is recognized early, usually within the first year of life. These findings support maternal-age-based counseling while indicating that neonatal recognition of trisomy 21 is already effective locally.

Introduction

Down syndrome, caused by trisomy of chromosome 21, is the most common autosomal aneuploidy compatible with survival and the leading genetic cause of intellectual disability, with a birth prevalence of roughly one per 700 to 1,000 live births [1-3]. It arises through three cytogenetic mechanisms with different origins and recurrence implications: free (regular) trisomy 21, which represents about 95.0% of cases and results from meiotic non-disjunction that increases sharply with maternal age; Robertsonian translocation, some 3.0% to 4.0%, a share of which is inherited from a balanced-carrier parent and carries a substantial recurrence risk; and mosaicism, roughly 1.0% to 2.0% [1, 2, 4]. Distinguishing these subtypes is therefore not academic: It determines whether parental karyotyping and recurrence-risk counseling are indicated [5].

The distribution of subtypes and the associated maternal-age profile are shaped by local demography and by how and when patients reach cytogenetic services. In populations with later maternal childbearing, the maternal-age association predicts a higher proportion of free trisomy [2, 6]. For Libya, early work established that trisomy 21 was overwhelmingly free trisomy and linked to advanced maternal age [7], and later Libyan and regional reports documented the associated burden of congenital heart disease and thyroid dysfunction [8-10]. A recent series from a Benghazi laboratory described the subtypes of Down syndrome over a period overlapping the present one [11], but the age at which patients are diagnosed, a marker of how promptly the condition is recognized, has not been reported for the region. This study examined the Down syndrome cases within a five-year cytogenetic registry at the Genome Laboratory in Benghazi; the present analysis focuses specifically on the Down syndrome cohort. The objectives were to describe the distribution of cytogenetic subtypes, to determine the age at which Down syndrome was diagnosed, and to characterize maternal age, including its comparison with other referred patients.

Materials and methods

Study design, setting, and cohort: This retrospective study analyzed the Down syndrome cases identified among all patients referred for chromosomal analysis to the Genome Laboratory, Faculty of Biomedical Sciences, University of Benghazi, between 2021 and 2025. These cases are the Down syndrome subset of a 319-record cytogenetic registry whose overall cytogenetic profile and abnormality spectrum are reported separately. The present data are confined to the analyses of the Down syndrome cohort. Records were anonymized before analysis and contained no patient-identifiable information.

Cytogenetic analysis and classification: Peripheral-blood lymphocytes were cultured for 72 hrs in RPMI-1640 medium supplemented with fetal bovine serum, L-glutamine, penicillin-streptomycin, and phytohemagglutinin-M at 37 °C. Cell division was arrested with colcemid, after which cultures were exposed to hypotonic 0.075 M potassium chloride and fixed in 3: 1 methanol-glacial acetic acid. Metaphase spreads were prepared on glass slides and G-banded by trypsin-Giemsa.

Karyotypes were examined by light microscopy and described according to the International System for Human Cytogenomic Nomenclature (ISCN) [12]. Down syndrome was confirmed by the presence of trisomy 21 and classified as free (regular) trisomy 21, Robertsonian or other translocation, or mosaic, based on the reported karyotype. Approximately 20 metaphase cells were examined per case at standard (non-high-resolution) banding resolution, and 3 to 5 metaphases were fully karyotyped. When mosaicism was suspected or detected, the number of cells examined was increased to 50.

Variables and statistical analysis: Recorded variables were sex, age at diagnosis (the age at karyotype referral), cytogenetic subtype, maternal and paternal age, parental consanguinity, and place of residence. Age at diagnosis was summarized as the median with interquartile range (IQR) and as the proportion diagnosed before one year. Subtype proportions are reported with 95.0% Wilson confidence intervals. Maternal age was compared between Down syndrome and other referred patients using the Mann-Whitney U-test.

Because the translocation (n = 3) and mosaic (n = 1) subgroups were small, subtype-specific comparisons are descriptive only. A two-sided p-value below 0.05 was considered significant; analyses were performed using IBM SPSS Statistics version 26.0. The study used anonymized laboratory karyotype records that contained no patient-identifiable data. Institutional permission to use the anonymized dataset for research purposes was granted by the laboratory (Genome Laboratory, subsequently merged into First International Laboratory, Benghazi, in 2023; approval reference no. 26/91) and (Reference no. 018-MJ-03-06-2026). Because the study used fully anonymized retrospective records containing no patient-identifiable information, informed consent was waived.

Results

Cohort and cytogenetic subtypes: Of the 319 records in the registry, 251 patients had an interpretable karyotype. Of these 251 patients, 58 (23.1%) had Down syndrome. The cohort comprised 31 males and 27 females (male-to-female ratio 1.15: 1). Free trisomy 21 accounted for 54 cases (93.1%; 95.0% CI: 83.6-97.3), translocation for three (5.2%), and mosaicism for one (1.7%; 95% CI: 0.3-9.1), as detailed in **Tables 1** and **2,** and **Figure 1**.

Table 1: Characteristics of the Down syndrome cohort

Characteristic	Category	n (%)
Sex	Male	31 (53.4)
	Female	27 (46.6)
Cytogenetic subtype	Free trisomy 21	54 (93.1)
	Translocation	03 (05.2)
	Mosaic	01 (01.7)
Age at diagnosis	Neonate (< one month)	28 (48.3)
	Infant (one month ≤ 2 yrs)	22 (37.9)
	Child (2 - 11 y)	05 (08.6)
	Adolescent (12 - 17 yrs)	01 (1.7)
	Not recorded	02 (03.4)
Region	Cyrenaica (East)	25 (43.1)
	Fezzan / South	02 (03.4)
	Not recorded	31 (53.4)
Year	2021	07 (12.1)
	2022	07 (12.1)
	2023	16 (27.6)
	2024	23 (39.7)
	2025 (partial)	05 (08.6)

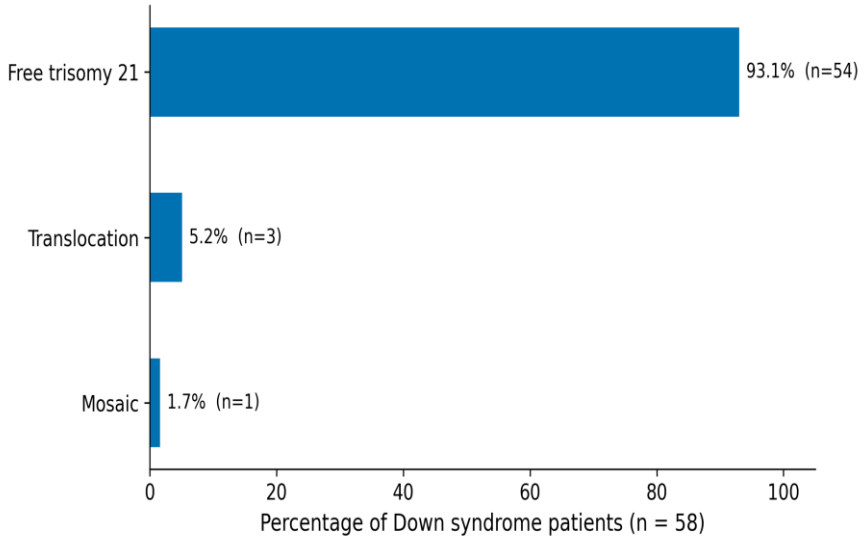

Figure 1: Distribution of Down syndrome cytogenetic subtypes

Table 2: Cytogenetic subtypes with representative karyotypes.

Subtype	n	% (95% CI)	Representative karyotype
Free trisomy 21	54	93.1 (83.6 - 97.3)	47,XX,+21 / 47,XY,+21
Translocation	03	5.2 (1.8 - 14.1)	46,XY,der(14;21)(q10;q10),+21
Mosaic	01	1.7 (0.3 - 9.1)	mos 47,XY,+21[16]/46,XY[4]

Age at diagnosis: Down syndrome was diagnosed early. Among the 56 patients with a recorded age, the median age at karyotyping was 0.10 years (approximately five weeks; IQR 0.04-0.33), and 50 (89.3%) were diagnosed before one year of age. Almost half of the cohort (28, 48.3%) was diagnosed in the neonatal period and a further 22 (37.9%) in infancy, with only six patients diagnosed after the second birthday (**Figure 2**). This early recognition contrasts sharply with the sex-chromosome aneuploidies identified in the same registry, which were diagnosed at a median age of 9.0 years for Turner syndrome and 29.0 years for Klinefelter syndrome.

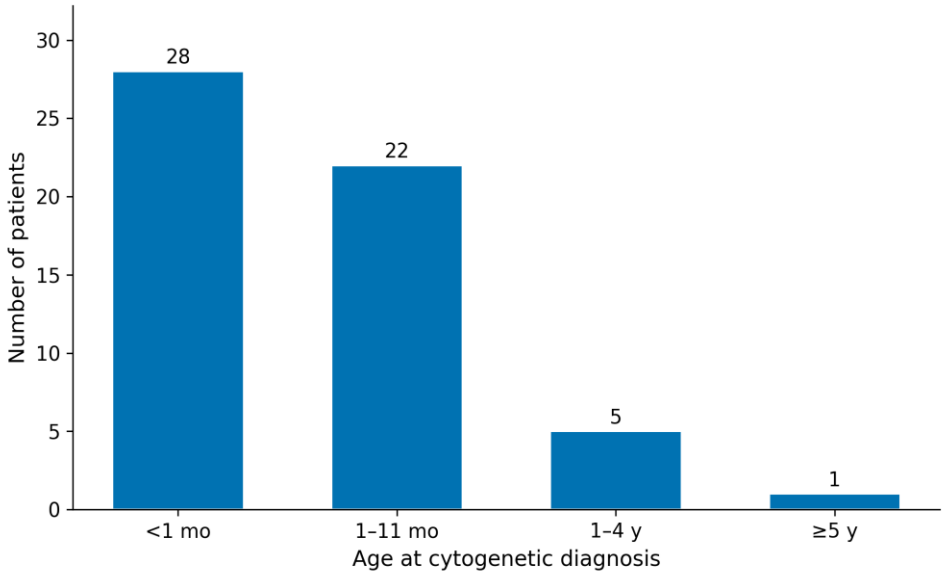

Figure 2: Age-related distribution at cytogenetic diagnosis of Down syndrome

Maternal and paternal age: Maternal age was recorded for 29 patients. The median maternal age was 37.0 years (IQR 31-41; range 22-48), and 17 mothers (58.6%) were aged 35 years or older. Maternal age was significantly higher than among the other referred patients in the registry (median 31.0 years, IQR 27-37, n = 77; Mann-Whitney U-test, p = 0.008) (**Figure 3**). Within subtypes, the 28 free-trisomy cases with a recorded maternal age had a mean of 36.1 years; the single translocation case with a recorded maternal age was 26 years, and no mosaic case had a recorded maternal age, so subtype-specific comparison was not possible. Paternal age, recorded for 29 patients, averaged 41.2 years (standard deviation 10.2) (**Table 3**).

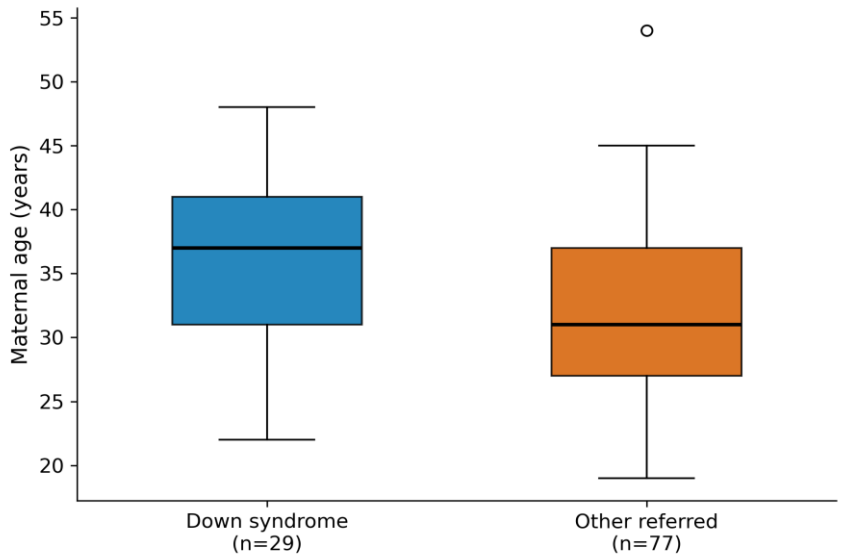

Figure 3: Maternal age in Down syndrome versus other referred patients

Table 3: Maternal and paternal age in the Down syndrome cohort

Variable	Frequency	Value
Maternal age, median (IQR)	29	37.0 (31 - 41) years
Aged ≥ 35 years	29	17 (58.6%)
Free trisomy 21, mean	28	36.1 years
Maternal age, other referrals, median (IQR)	77	31.0 (27 - 37) years
Down versus other	-	**p = 0.008**
Paternal age, mean (SD)	29	41.2 (10.2) years

Consanguinity and comparison with other series: Parental consanguinity was recorded for 25 of the 58 families, of whom five were consanguineous; the high proportion of unrecorded status and the small translocation subgroup preclude a meaningful test of the reported association between consanguinity and translocation, which is therefore not analyzed here. The subtype distribution observed in this cohort is compared with earlier Libyan data, a recent Benghazi series, and international reference ranges in **Table 4**.

Table 4: Distribution of Down syndrome cytogenetic subtypes across studies

Study (setting, n)	Free trisomy	Translocation	Mosaic	Notes
This study (Genome Lab, Benghazi; n = 58)	93.1%	5.2%	1.7%	2021 - 2025
Amer et al. [11] (First Intl Lab, Benghazi; n = 200)	82.0%	6.0%	12.0%	2020 - 2025 [11]
Verma et al. [7] (Libya)	≈ 96%	-	-	historical [7]
International reference range	≈ 95%	3.0% - 4.0%	1.0% - 2.0%	[1, 2]

Dashes indicate subtype detail not separately reported

Discussion

Among cytogenetic referrals in eastern Libya, Down syndrome was predominantly free trisomy 21 (93.1%), with translocation and mosaic forms together accounting for fewer than one in fourteen cases. This distribution is consistent with international reference ranges and with the earliest Libyan cytogenetic data, in which trisomy 21 was almost entirely free trisomy [1, 2, 7]. It differs, however, from a recent series at the First International Laboratory in Benghazi, which reported trisomy 21 in 82.0%, mosaicism in 12.0%, and translocation in 6.0% of 200 cases sampled over an overlapping period [11]. The divergence is largest for mosaicism, reported at 1.0% to 2.0% in most large series and found in 1.7% here; the 12.0% figure most plausibly reflects differences in case ascertainment and in the number of metaphases scored rather than a true local excess. That two Benghazi series drawn by different methods, a full count of consecutive cases here versus systematic every-third-record sampling there, both identify free trisomy 21 as the dominant subtype supports this profile for the region even as their exact proportions differ.

The most distinctive finding is how early Down syndrome was diagnosed: The median age at karyotyping was about five weeks, and nearly nine in ten patients were confirmed before their first birthday. This indicates that the clinical features of trisomy 21 are recognized promptly at or shortly after birth and are acted on with confirmatory karyotyping. The contrast with the sex-chromosome aneuploidies in the same registry (median age at diagnosis 9.0 years for Turner syndrome and 29.0 years for Klinefelter syndrome [13-15]) is marked, and locates the diagnostic gap in Libyan cytogenetic services among the subtler disorders that present through short stature, pubertal delay, and infertility rather than the obvious neonatal syndromes. This pattern of prompt neonatal recognition contrasts with reports from other low- and middle-income settings, where limited antenatal screening infrastructure has been linked to later or incidental detection of Down syndrome [16].

Maternal age in the cohort was high (median 37.0 years; 58.6% aged 35 years or older) and significantly exceeded that of other referred patients, reproducing the best-established risk factor for trisomy 21 [5, 6] and matching the advanced maternal age reported in the earlier Libyan series [7]. In a population with a tendency

toward later childbearing and frequent consanguineous marriage [17-19], this supports maternal-age-based counseling and the consideration of prenatal screening for older mothers. The cohort was underpowered to test the reported link between consanguinity and translocation Down syndrome, a relationship that would require a dedicated, adequately sized study. This analysis shares the limitations of the parent registry: Retrospective and single-laboratory, it reflects referral practice rather than the birth population, so prevalence cannot be estimated. Maternal age was missing for about half of patients, leaving that comparison to rest on 29 cases, and the consanguinity and geographic findings are descriptive. The translocation and mosaic subgroups were too small for subtype-specific inference or parental-karyotype follow-up, and age at diagnosis reflects the age at referral rather than first clinical suspicion. Thus, strengthening genetic counseling for older mothers and for families affected by translocation, together with parental karyotyping where indicated, would build on this foundation.

Conclusion: In eastern Libya, Down syndrome is overwhelmingly free trisomy 21, is strongly associated with advanced maternal age, and is diagnosed early, usually within the first year of life. The free-trisomy-dominant profile agrees with international and historical Libyan data and with a further local series from the same Benghazi laboratory setting, while the early age at diagnosis shows that neonatal recognition of trisomy 21 is already effective.

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